

## **Painful bladder syndrome**

'Interstitial cystitis' first described by Skene in 1887

*Complex of voiding symptoms attributable to a functionally reduced bladder capacity*

ICS prefers term painful bladder syndrome:

*The complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology* (Abrams 2002)

ICS definition emphasises central role for painful bladder filling

### Demographics

Incidence estimated at 230 per 100,000 Finnish population (Leppilahti 2005)

Female: male 10:1

Median age 40-50 yrs

Caucasians > blacks

Presentation

Bladder pain, usually accompanied by urgency, frequency, nocturia  
Typically subacute development, with relatively rapid deterioration in symptoms, followed by more gradual worsening or plateau  
Spectrum of severity from mild urgency-frequency syndrome (no fibrosis, little pain) through to severe bladder pain with decreased bladder capacity (due to fibrosis)

Aetiology

Cats provide reasonable animal model for PBS/IC

Many theories postulated; probably multifactorial

(i) Chronic infection

Either persistent (minimal evidence to suggest ongoing infection)  
or leading to an autoimmune reaction (raised ANA often seen)

(ii) Reflex sympathetic dystrophy

Increased sympathetic upregulation in PBS/IC

(iii) Neuroinflammation

Abnormal neurogenic mechanism leading to upregulation of sensory nerve inputs and 'neuroinflammation'

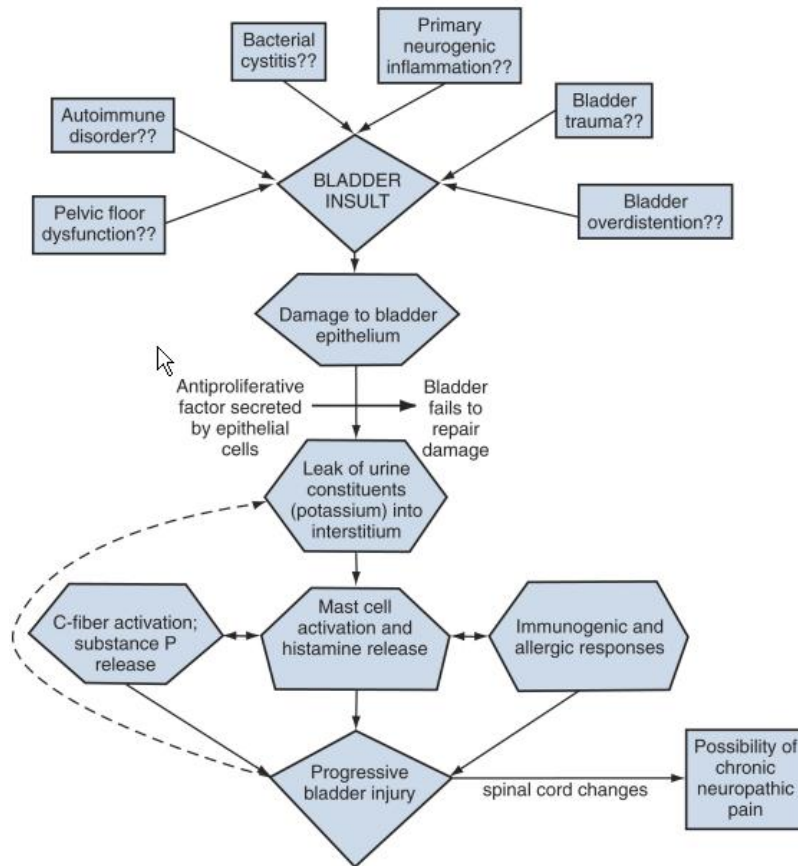
(iv) Defective glycosaminoglycan layer

Popularised by Parsons

Reduced GAG layer allows leakage of urine into urothelium.  
Toxic molecules (?potassium) within urine then depolarise sensory nerves and muscle, leading to pain and urgency. As potassium is an endogenous waste product, explains lack of inflammation

(v) Antiproliferative factor

Frizzled 8 protein produced by bladder uroepithelial cells.  
Inhibits heparin binding EGF important for epithelial repair.  
Urinary levels increased in patients with PBS/IC, reduced after hydrodistension. Good sensitivity/specificity for identification of PBS/IC



## Pathology

Glomerulations = pinpoint petechial mucosal haemorrhages

Hunner's ulcer = discrete area of mucosal ulceration seen in 6-8% IC cases

## Biopsies

Typically show very little evidence of chronic inflammation; occasionally chronic inflammatory cells in lamina propria

Mucosa thin – often only 2-4 cell layers thick (vs. 7-8 normally), but most biopsies performed after hydrodistension ?artifact

Mast cells seen in ~ 30% of biopsies. Mast cell degranulation thought to increase epithelial permeability and sensitive nerve endings

## Cystectomy specimens

80% have only epithelium, with occasional muscle fibres and BV, with thinning of perivesical fat. Widespread collagenous replacement of bladder wall is not typically a feature

## Diagnosis

### Interstitial cystitis is a diagnosis of exclusion

Other causes of IC-type voiding symptom complex

Infective	Bacterial, viral, fungal, schistosomal or TB cystitis Sexually transmitted infections
Inflammatory	Radiation or cyclophosphamide cystitis Amyloidosis
Neoplastic	CIS, other bladder Ca, urethral cancer

Anatomic                      Cystocoele, urethral obstruction

#### NIDDK criteria

National Institute for Diabetes, Digestive and Kidney Diseases  
Developed criteria for identification of PBS/IC patients in 1998  
Used to identify patients for research criteria, not for diagnosis  
High specificity but low sensitivity – misses up to 2/3 patients  
NIADDK criteria only designed to identify severe group

##### Inclusion criteria (2)

Bladder pain or urgency AND  
Glomerulations\* or Hunner's ulcer

##### Exclusion criteria (18)

Child < 18 yrs  
Duration < 9 months  
Daytime frequency < 8  
Absence of nocturia

##### UDS (3)

Maximum cystometric capacity >350ml  
Absence of urge with bladder filled to 150ml  
Phasic contractions on filling

##### Infective (5)

Symptoms relieved by antibiotics/anticholinergics  
Recent confirmed UTI or prostatitis  
TB cystitis  
Active genital herpes  
Vaginitis

##### Inflammatory (2)

Radiation cystitis  
Cyclophosphamide or other chemical cystitis

##### Neoplastic (2)

Bladder tumour (benign or malignant)  
Uterine, Cx, vaginal or urethral cancer

##### Anatomic (2)

Urethral diverticulum  
Bladder or ureteric calculi

\* distension of bladder under anaesthesia at pressure of 80-100cm water for 1-2 minutes. May be repeated x1 before assessment. Glomerulations must be diffuse (in all 4 quadrants) for diagnosis

#### Investigation

##### History

Exclude alternative diagnosis  
IC more common in those with Hx atopy, IBS, fibromyalgia

##### Vaginal examination

Tender bladder base anteriorly in >90% (Parsons)  
Urethral diverticulum  
Cystourethrocoele  
Vaginal discharge

MSU

Additional urine investigation if TB or schistosomiasis suspected

Cytology

Parsons found no positive cytology in >3000 cases)

Urodynamics

EUA, cystoscopy, diagnostic hydrodistension and bladder biopsy

Bladder biopsy controversial, but finding of mast cells in biopsy may consolidate diagnosis (20% non-ulcer patients; 65% ulcer patients)

Potassium chloride test

0.4M intravesical KCl a/w reproduction of pain

However multiple problems

Supraphysiologic [K+]

10x natural concentration of K+ in urine (40MEq/l)

Poor sensitivity

Misses 25% NIDDK patients!

Poor specificity

positive in UTI, radiation cystitis, prostatitis, pelvic pain

**Urinary antiproliferative factor** (APF; Susan Keay, U of Maryland)

94% sensitive (NIDDK positive patients) and 79% specific (Keay 2001) – promising but more studies needed

Management (from Fall 2008: best evidence)

May be conservative, oral, intravesical or surgical

(a) Conservative

(i) Bladder drill

(ii) Avoidance of precipitants

Approximately 50% experience spontaneous temporary remission in symptoms

(b) Oral therapy

(i) **Amitriptylline**

Best study van Ophoven (2004). PC-RCT showing significantly improved symptom score, pain and urgency with self titrated amitriptylline 25-100mg. Follow-up open label study showed 64% response rate at 20 months (mean dose 55mg). Side effects generally drowsiness and other anticholinergic effects

(ii) Pentosan polysulphate (Elmiron; 150 mg bd)

Heparinoid polysaccharide

Overall some benefit identified in RCTs. Largest study Nickel (2005; n=380) showed ~50% response rate at 6 months with 300mg a day. Side effects mild.

(iii) Cimetidine

H2 receptor blocker. Best study Thilagarajah 2001; 65% response rate with 400mg bd. Usage limited by side-effects (N+V, diarrhoea, impotence, gynaeomastia, long Q-T interval) and drug interactions (phenytoin, warfarin, theophylline)

(iii) Hydroxyzine

H1 histamine receptor antagonist – blocks release of histamine from mast cells

Initial reports of > 90% response with 25-50mg dosage. Only one third of patients respond in PC-RCTs. May be better in subpopulation with pre-existing atopy

(iv) Cyclosporin A

Significantly better when compared in RCT vs. PPS but side effect profile worse

(c) Intravesical therapy

(i) **Dimethyl sulphoxide (DMSO)**

Chemical solvent believed to have analgaesic, anti-inflammatory, collagenolytic and muscle relaxant effects  
Best study Perez-Marrero (1988). PC-RCT showing improved symptom score, pain score and UDS data in 93% pts receiving DMSO (? regime/dose get paper) vs. 35% on placebo. High relapse rates of 59%; ? reduced by monthly instillations of intravesical heparin (same group 1993).

(ii) Sodium hyaluronate

Aka. Cystistat

Response rate ~70%

(iii) Chondroitin sulphate

(iv) Pentosan polysulphate

(d) Surgical

No RCTs available to support surgical management of IC

(i) Hydrodistension

Reported 50-60% initial remission rate with Helmstein technique but relapse rate high. Largest trial Glemain 2002 - no placebo group, hydrodistension under epidural for 3 hours a/w 33% efficacy at 1 year. Few centres perform Helmstein due to risk of bladder rupture and necrosis. Short-duration (5 mins ~@ 80-100cm water) hydrodistension reportedly as effective as long-term but effects very short-lived (< 6mo.)has any effect.

(ii) TUR Hunner's ulcer

Peeker 2000 - 90% improvement in Sx following TUR of ulcer, 40% had Sx relief at 3 yrs; Malloy 1994 largest trial of laser fulguration - improved Sx in 33-78% of patients, effects most marked in ulcer group.

(iii) Botox therapy

Promising but unrandomised data so far

(iv) Sacral nerve modulation

Peters et al 2004 (n=34) with permanent implant, > two thirds improved symptom and pain score

(v) Augmentation cystoplasty

Supratrigonal cystectomy and enterocystoplasty.

75% pain free; ileocaecal a/w lower ISC than ileal; small capacity (< 250ml) had better functional outcome than larger capacity

(vi) Urinary diversion

Cystectomy and urinary diversion for intractable cases - more effective in patients with capacity < 400 (Lotenfoe 1995).

Urethral syndrome

*Signs and symptoms of UTI without positive urine cultures.*

More than one study has reported that in patients with signs and symptoms of UTI, negative cultures are found in ~50% (Gallagher 1965; Hamilton-Miller 1994). May represent one of the many causes of irritative LUTS or indeed mild IC. Continued usage of the term urethral syndrome discouraged.